17. (Three Times Amended) A LM609 CDR-grafted light chain polypeptide comprising a variable region amino acid sequence having [greater than 88%] 79% or greater identity with that shown in Figure 1B (SEQ ID NO:4) or a functional fragment thereof, wherein said variable region amino acid sequence encoding said light chain polypeptide is a non-mouse sequence and wherein an antibody comprising said light chain polypeptide has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity, or integrin $\alpha_v\beta_3$-inhibitory activity.

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REMARKS

Claims 1-18 and 26-31 are under examination in the application. Claims 1, 3, 4, 6, 7, 9, 12, 15, and 17 have been amended. Support for the amendment can be found throughout the specification. In particular, support for the amendment to claims 1, 9, 12, 15 and 17 can be found, for example, on page 8, line 15, to page 9, line 16; page 20, line 22, to page 22, line 10; and page 45, lines 5-8. Support for the amendment to claims 3, 4, 6 and 7 can be found, for example, on page 17, lines 21-26. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested. Entry of the proposed amendment is respectfully submitted to be proper because the amendment is believed to place the claims in condition for allowance.

Applicant appreciates the time and helpful discussion with Applicant's representatives and Examiner Gambel held in the telephonic interview on April 11, 2000.

The present invention provides a LM609 CDR-grafted antibody comprising at least one heavy chain polypeptide comprising a variable region amino acid sequence shown in Figure 1A (SEQ ID NO:2), where the variable region amino acid sequence has a framework sequence having 88% or greater identity with the framework sequence of SEQ ID NO:2, and at least one light chain polypeptide comprising a variable region amino acid sequence shown in Figure 1B (SEQ ID NO:4), where the variable region amino acid sequence has a framework sequence having 79% or greater identity with the framework sequence of SEQ ID NO:4. The antibodies of the invention are non-mouse antibodies or functional fragments thereof that contain heavy and light chain CDR amino acid sequences derived from LM609 and have integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Nucleic acids encoding LM609 CDR-grafted antibody heavy and light chains are additionally provided. Applicant has reviewed the Office Action and respectfully traverses all grounds for rejecting the claims for the reasons that follow.

Double Patenting Rejection

Claims 1-18 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly unpatentable over claims 1-48 of copending application serial number 08/791,391. Applicant respectfully requests that this provisional ground of rejection be deferred until there is an indication of allowable subject matter.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 9, 10, and 12-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description in that the disclosure does not reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. The Office Action alleges that the specification does not provide support for the claims "having greater than 88%/79% identity."

Applicant respectfully submits that the specification provides sufficient written description to convey to one skilled in the art that Applicant had possession of the claimed invention at the time the application was filed. Claims 1, 9, 12, 15 and 17, as amended, are directed to a LM609 CDR-grafted antibody and a LM609 CDR-grafted heavy or light chain polypeptide, or encoding nucleic acids, having a framework sequence having 88% or greater identity with SEQ ID NO:2 or 79% or greater identity with SEQ ID NO:4, respectively. Support for the phrases "said variable region amino acid sequence having a framework sequence having 88% or greater identity with that shown in Figure 1A (SEQ ID NO:2)" and "said variable region amino acid sequence having a framework sequence having 79% or greater identity with that shown in Figure 1B (SEQ ID NO:4)" can be found, for example, on page 45, lines 5-8, and on page 20, line 22, to page 22, line 10.

In particular, the specification teaches that the human heavy chain variable region M72 'CL had 88% identity with frameworks 1, 2 and 3 of LM609 heavy chain and human light chain

V region LS1 'CL had 79% identity to frameworks 1, 2 and 3 of LM609 light chain (page 45, lines 5-8). The specification also teaches that any or all of the non-identical amino acids can be changed either alone or in combination with amino acids at different positions to incorporate the desired number of amino acid substitutions at the desired positions (page 20, lines 22-27). Therefore, the specification teaches that any or all of the non-identical amino acids, i.e., any or all of the 12% non-identical amino acid residues that differ between the human framework and LM609 heavy chain, can be modified, which results in a heavy chain polypeptide variable region amino acid sequence having a framework sequence having 88% or greater identity to the human framework sequence of SEQ ID NO:2. Similarly, the specification teaches that any or all of the 21% non-identical amino acid residues that differ between the human framework and LM609 light chain can be modified, which results in a light chain polypeptide variable region amino acid sequence having a framework sequence having 79% or greater identity to the human framework sequence of SEQ ID NO:4. The specification further teaches that the LM609 CDR-grafted antibody is a non-mouse antibody, as specifically recited in the claims (see page 8, line 15, to page 9, line 16).

In regard to functional fragments of the claimed LM609 CDR-grafted antibodies and heavy and light chain polypeptides, the specification teaches that a functional fragment is a portion of a LM609 grafted antibody including heavy or light chain polypeptides which still retains some or all of the $\alpha_v\beta_3$ binding activity, $\alpha_v\beta_3$ binding specificity and/or integrin $\alpha_v\beta_3$-inhibitory

activity (page 14, lines 4-10). In regard to the nucleic acids, the specification teaches that the invention provides a nucleic acid encoding a heavy chain and light chain for a LM609 grafted antibody (page 14, line 24-28). The claims reciting 88% or 79% identity with the framework sequence of a specifically recited SEQ ID NO also recite functional characteristics of an antibody containing a polypeptide encoded by the nucleic acid, specifically that the antibody has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity, or integrin $\alpha_v\beta_3$-inhibitory activity. Such functional activities of the antibody are specifically recited in the claims and, in regard to modification of non-identical residues in a human framework sequence relative to LM609, the specification teaches that the LM609 CDR-grafted polypeptides containing desired substitutions of non-identical amino acids can be screened for activity (page 20, line 22, to page 21, line 1, and page 21, line 21, to page 22, line 1).

Applicant respectfully submits that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicant had possession of the claimed invention at the time the application was filed. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 3-8 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the phrase "or a modification thereof that does not change the encoded amino acid

sequence." Applicant respectfully submits that the meaning of this phrase is clear and definite. Nevertheless, the claims reciting the phrase have been amended to indicate that the modification is of the nucleotide sequence and the modification does not change the encoded amino acid sequence.

The Office Action has indicated that the claims should be amended to recite the nature of the modifications to distinctly claim the invention and to distinguish the modification thereof from the sequence itself. Applicant respectfully submits that the claims already recite the nature of the modifications, specifically, modifications that do not change the encoded amino acid sequence. As described on page 17, lines 21-26, a minor modification of a nucleotide sequence can include changes which do not change the encoded amino acid sequence due to degeneracy of the genetic code. The description on page 17, lines 21-28, describes two types of minor modifications, "those which do not change the encoded amino acid sequence due to the degeneracy of the genetic code as well as those which result in only a conservative substitution of the encoded amino acid sequence." Although a modification can include both, the claims specifically recite the nature of the modification, that the modification does not change the encoded amino acid sequence. Therefore, Applicant submits that the rejection is moot and that the claims reciting a modification of a nucleotide sequence are clear and definite. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C. § 102

An issue of public use or on sale activity has been raised under 35 U.S.C. § 102(b). Applicant respectfully maintains that the claimed LM609 CDR-grafted antibody and encoding nucleic acids were not in public use or on sale in this country more than one year prior to the filing date of the above-identified application.

The lack of on sale or public use activity was corroborated by evidence presented in the form of Declarations by Dr. Huse in the previous responses mailed December 9, 1998, and September 20, 1999. Applicant appreciates the Examiner's acknowledgment that the previous arguments and evidence sufficiently addressed the confidentiality and control of Ixsys in interactions with Celltech Biologics and withdrawal of the public use and on sale rejection with respect to Ixsys and Celltech Biologics.

The Office Action indicates that Applicant has not set forth restrictions or confidentiality with respect to the Scripps Research Institute (hereinafter Scripps) and principle investigator Dr. Cheresh as it applies to public use and on sale activity. First, as Applicant has previously contended, the cited Biotechnology Newswatch publications are insufficient to constitute a public use or sale of the claimed invention either by Applicant or by a third party. In this regard, mere knowledge of an invention by the public does not warrant rejection under 35 U.S.C. § 102(b) as the bar is to public use or sale and not to

public knowledge. TP Labs, Inc. v. Professional Positioners, Inc., 724 F.2d 965, 970, 220 USPQ 577, 581 (Fed. Cir. 1984).

Second, neither of the Biotechnology Newswatch publications places the claimed invention in the public domain as neither Biotechnology Newswatch publication recites the specifically claimed nucleotide or amino acid sequences. In particular, there is no description of the nucleotide or amino acid sequences of the claimed CDRs nor of the claimed framework changes.

Third, in regard to the role of the third parties Scripps and Dr. Cheresh, the Biotechnology Newswatch publications are similarly insufficient to provide a basis for a public use or on sale rejection under 35 U.S.C. § 102(b). To qualify as prior art, the item must place the claimed features in the public possession before the critical date. Lockwood v. American Airlines, Inc., 41 USPQ 2d 1961, 1964-65 (Fed. Cir. 1997). The Biotechnology Newswatch publications are contradictory in that the later published article, directed to the Celltech agreement, indicates that a humanized antibody is still being developed (Biotechnology Newswatch, February 6, 1995, page 11, second to last paragraph). Moreover, the earlier Biotechnology Newswatch publication describes that third parties Scripps and Dr. Cheresh published data in regard to the mouse monoclonal antibody LM609 (Biotechnology Newswatch, January 16, 1995, page 12, column 1, paragraphs 3 and 9). However, it was the company, Ixsys, that developed a humanized version of the antibody (page 12, column 2, paragraph 2). Together, these publications cannot form a proper

basis for rejection under the public use or on sale bar because they lack any indication that any of the claimed sequences were in possession of a third party. Instead, these publications show that either the claimed invention was still being developed or that it was developed by the company, Ixsys.

Finally, the Biotechnology Newswatch publication of January 16, 1995, itself describes that the third party Scripps licensed the rights to Ixsys to modify the mouse LM609 antibody and to use it, and that the company, Ixsys, developed the humanized version (page 12, second column, paragraphs 1 and 2). Such a description does not raise sufficient issues of control or confidentiality to form a basis of rejection under 35 U.S.C. § 102(b) as a public use or on sale bar. Instead, the January 16, 1995, publication only reports positive results by Scripps using the mouse antibody, that Scripps transferred rights to Ixsys to develop a humanized form, and that the company proceeded to develop the humanized form.

In light of the above and in contrast to the assertions in the Office Action, Applicant maintains that neither Biotechnology Newswatch publication describes any claimed feature of the claimed invention, including the humanized version of the antibody. A mere statement that such an antibody may exist is insufficient to establish public use or sale. Moreover, the objective evidence of record is insufficient to raise an issue of public use without restriction or obligation of secrecy to the invention. Therefore, Applicant maintains that the cited

Biotechnology Newswatch publications are insufficient to raise an issue of public use or on sale activity.

In light of the above remarks, Applicant respectfully maintains that the claimed LM609 CDR-grafted antibody and encoding nucleic acids were neither on sale nor in public use in this country more than one year prior to the filing date of the above-identified application. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Claims 1-18 and 26-31 stand rejected under 35 U.S.C. § 102(f) because Applicant allegedly did not invent the claimed subject matter. The Office Action alleges that Applicant's arguments, the Huse Declaration filed in the response mailed December 9, 1998, U.S. Patent 5,753,230, issued May 19, 1998 (Brooks et al.), and the Biotechnology Newswatch article dated January 16, 1995, present an ambiguity with regard to the inventorship of the claimed invention.

In regard to the Declaration by Dr. Huse submitted with the response mailed December 9, 1998, this previously filed Declaration was directed to the issue of alleged public use or on sale activity, not to inventorship. The statement of conception in this Declaration by Dr. Huse was there to put in perspective the relationship of how certain materials were obtained and maintained under the control of Ixsys. Accordingly, the assertion that Dr. Huse's Declaration indicated sole conception is misconstrued and out of context, as the only statements of record directed to inventorship have been by Applicant's

representative, that inventorship has been reviewed and determined to be correct. Therefore, the Huse Declaration submitted December 9, 1998, presents no ambiguity with regard to inventorship.

Applicant maintains that inventorship has been reviewed and determined to be correct. However, to further prosecution, Applicant submits herewith a Declaration by Dr. Huse (Exhibit 1) attesting that he is the sole inventor of the claimed LM609 CDR-grafted antibody and encoding nucleic acids.

In regard to Dr. Glaser, the Declaration by Dr. Huse submitted herewith as Exhibit 1 unequivocally states that Dr. Huse is the sole inventor of the claimed LM609 CDR-grafted antibody and encoding nucleic acids. The Declaration attests that Dr. Huse conceived the claimed LM609 CDR-grafted antibody and encoding nucleic acids. Applicant respectfully disagrees with the assertion on page 5 of the Office Action that Applicant has determined that both Huse and Glaser are inventors of the claimed compositions. Applicant has never asserted that Dr. Glaser is an inventor of the claimed compositions of the above-identified application. Therefore, Applicant maintains that inventorship of the above-identified application is correct, as corroborated by Dr. Huse's Declaration (Exhibit 1).

In regard to Dr. Cheresh and Dr. Brooks, the Declaration attached herewith as Exhibit 1 clearly indicates that neither Dr. Cheresh nor Dr. Brooks suggested or contributed to the cloning, sequencing, humanizing or making of the claimed

antibodies and nucleic acids. In regard to Dr. Cheresh's role, the Declaration indicates that Dr. Cheresh was retained for technical advice on integrin biology. There was no collaboration between inventor Huse and Dr. Cheresh with respect to conception and reduction to practice of the claimed antibody and nucleic acid sequences. Furthermore, the Declaration clearly states that the sequencing of the LM609 encoding nucleic acids and generation of LM609 grafted antibodies were carried out at Ixsys, Inc. Since the cloning and sequencing of LM609 and the making of the claimed LM609 CDR-grafted antibody were conducted at Ixsys under their control and without contribution by Dr. Cheresh or Dr. Brooks, Applicant respectfully submits that neither Dr. Cheresh nor Dr. Brooks can be considered inventors of the claims directed to antibodies and encoding nucleic acids reciting specific SEQ ID NOS.

In regard to conception of a nucleic acid sequence, the question of when conception of a nucleic acid chemical compound has been conceived has been examined by the federal court in Amgen v. Chugai Pharmaceutical, 927 F.2d 1200 (Fed Cir. 1991). The federal circuit court held

> We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. (Id. at 1206)

Applicant respectfully submits that, consistent with the federal court holding, there was no inventive contribution by Drs. Cheresh or Brooks to the claimed LM609 CDR-grafted antibody referenced as SEQ ID NOS:2 and 4 and encoding nucleic acids because conception and reduction to practice occurred at Ixsys without contribution by Drs. Cheresh or Brooks to the cloning or sequencing of LM609 encoding nucleic acids or to making and testing the claimed LM609 CDR-grafted antibody nucleic acids and polypeptides.

The Office Action continues to assert that it was possible to determine without undue experimentation humanized antibodies having the same properties as LM609 and in light of U.S. Patent No. 5,753,230, and the issue is raised as to why Drs. Cheresh and Brooks are not inventors of the claimed invention. As previously stated and averred to in the declaration attached as Exhibit 1, neither Drs. Cheresh nor Brooks contributed to the conception or reduction to practice of the claimed sequences. Any description of a humanized LM609 in U.S. Patent No. 5,753,230 is a statement of a problem to be solved because there is no completion of the mental part of the invention as such a description lacks a definite and permanent idea of the complete and operative invention. Coleman v. Dines, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985); Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d 1223, 1227, 32 USPQ 2d 1915, 1919 (Fed. Cir. 1994). As held in Amgen, conception of a gene is not complete until it has been reduced to practice (Id. at 1206). Therefore, absent a description in U.S. Patent No. 5,753,230 or other evidence of the LM609 nucleic acid

sequence, there is no issue of inventorship as to the claimed invention based on the cited patent.

In summary, Applicant respectfully submits that Dr. Huse is the inventor of the claimed LM609 CDR-grafted antibody and encoding nucleic acids, and therefore, that inventorship of the above-identified application is correct. Accordingly, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 102(f) be withdrawn.

Claim 26 stands rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Brooks et al., U.S. Patent No. 5,753,230. Applicant respectfully submits that the claimed LM609 CDR-grafted antibody is novel over Brooks et al.

Claim 26 is directed to a LM609 CDR-grafted antibody comprising a LM609 CDR-grafted heavy chain polypeptide encoded by a LM609 CDR-grafted heavy chain variable region nucleotide sequence referenced as SEQ ID NO:1, or a modification thereof, and a LM609 CDR-grafted light chain polypeptide encoded by a LM609 CDR-grafted light chain variable region nucleotide sequence referenced as SEQ ID NO:3, or a modification thereof, having integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity, as recited in claim 26. In contrast, Brooks et al. does not teach the claimed human acceptor framework sequences with LM609 CDRs encoded by the specifically recited nucleotide sequences referenced as SEQ ID NOS:1 and 3. Absent such a teaching of the structural features of the antibody specifically recited in the claim, Applicant respectfully submits

that Brooks et al. cannot anticipate the claim. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C § 103

Claims 1-18 and 26-31 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Brooks et al., U.S. Patent No. 5,753,230, in view of the known art of gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof. Applicant respectfully maintains that the claimed LM609 CDR-grafted antibody and encoding nucleic acids are unobvious over Brooks et al.

In regard to claims directed to LM609 CDR-grafted antibody, Applicant respectfully maintains that, in contrast to the claimed antibodies, Brooks et al. does not teach or suggest any of the structural features specifically recited in the claims, in particular, the specifically recited amino acid sequences referenced as SEQ ID NOS:2 and 4. Absent a description of the LM609 nucleotide sequence or the LM609 encoding CDR sequences, Brooks et al. cannot render the claimed invention obvious because the claims specifically recite sequences, each of which is one sequence out of many possible sequences that might have been obtained following methods known in the art. As described further below, such methods, in light of Brooks et al., do not provide a reasonable expectation of success for determining the claimed sequences.

Furthermore, Brooks et al. does not teach or suggest the claimed human acceptor framework sequences with LM609 CDRs corresponding to SEQ ID NOS:2 and 4. Therefore, Applicant respectfully submits that Brooks et al. does not teach or suggest the claimed antibodies having the structural characteristics of the specifically recited SEQ ID NOS.

Further in regard to the human acceptor framework changes in the claimed antibodies, the Padlan reference (Mol. Immunol. 28:489-498 (1991)), which is cited in the Office Action, describes a possible procedure for reducing the immunogenicity of antibody variable domains while preserving ligand binding properties by replacing exposed residues in the framework regions which differ from those usually found in host antibodies (see abstract, page 489 and paragraph bridging pages 489-490). Padlan also describes characterization of the solvent exposure of amino acid side chains of framework residues (page 490, first full paragraph and Tables 1-3).

In contrast to the assertion in the Office Action, Applicant submits that Padlan does not describe the same procedures as Applicant used to make the claimed LM609 CDR-grafted antibody. Padlan refers to solvent accessibility of framework residues, and such solvent exposed residues were not changed in Applicant's claimed antibodies. In contrast, Padlan describes replacing solvent exposed residues (see page 489, abstract, and paragraph bridging pages 489-490). Moreover, Padlan describes at least four examples where buried residues are specifically excluded from residues to be replaced (see pages 496

and 497, sections (a) and (b)). Therefore, one skilled in the art would not have been motivated, based on the description in Padlan, to generate the claimed antibodies having human acceptor framework changes, as with Applicant's claimed antibodies.

In regard to the alleged routine nature of cloning an immunoglobulin gene from a hybridoma, Applicant respectfully disagrees with the assertion on page 7, third paragraph, of the Office Action that "[G]iven the highly conserved nature of immunoglobulin gene organization and structure and the availability of probes and PCR primers for immunoglobulin gene cloning, one of ordinary skill in the art could have isolated the functionally rearranged heavy and light chain variable regions from the LM609 hybridoma cell line and determined their sequences with a complete expectation of success." At best, using such methods would have presented one skilled in the art with a need to further characterize any nucleic acid sequences obtained to ascertain which, if any, of the sequences corresponded to authentic cDNA for LM609. Applicant respectfully submits that it would not have been a matter of routine experimentation to generate chimeric or humanized LM609 antibodies and encoding DNA using probes and PCR primers, as alleged in the Office Action.

As evidence that the cloning of a variable region nucleotide sequence from a hybridoma cell was not routine, Applicant submits herewith a Rule 132 Declaration by Dr. Huse (Exhibit 2) attesting to the difficulties involved in cloning a variable region from a hybridoma cell using PCR primers to a conserved region in an immunoglobulin gene. The Declaration

further indicates that, to obtain Applicant's claimed sequences, amino acid sequencing of each variable chain was determined prior to designing PCR primers to clone cDNA encoding LM609 (see specification, page 39, lines 9-14). In light of the difficulties associated with cloning authentic cDNA sequence encoding the monoclonal antibody expressed by a hybridoma, as corroborated by the Declaration by Dr. Huse (Exhibit 2), Applicant respectfully maintains that the claimed compositions reciting specific SEQ ID NOS are unobvious over Brooks et al.

Further support for the difficulties associated with cloning authentic cDNA encoding a monoclonal antibody expressed in a hybridoma cell is provided in the reference by Morrison and Oi (Advances in Immunology 44:65-92 (1989)), which was cited by the Examiner in the telephonic interview held April 11, 2000, and proposed to support the statements in the Office Action regarding the state of the immunoglobulin art when a hybridoma is available. The Examiner pointed to page 73 of Morrison and Oi as support for the proposition in the Office Action that one does not need to determine the amino acid sequence of a rearranged V region before cloning. However, Morrison and Oi follow this assertion with an important caveat:

> Unfortunately, hybridoma cell lines often contain aberrantly rearranged variable region gene segments, some of which are transcribed; in these cases further characterization of the expressed variable region is required so that the correct gene can be identified. (page 73, first paragraph)(emphasis added)

that both decisions support the unobviousness of the claimed nucleotide sequences.

The Deuel Court framed the inquiry in terms of whether the combination of prior art reference teaching a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein, may render DNA and cDNA molecules encoding the protein prima facie obvious. Significantly, the Brooks '230 patent fails to provide even a partial amino acid sequence. In contrast, the Bohlen reference cited in combination with Maniatis in Deuel disclosed the N-terminal portion of the protein corresponding to appellants' claimed cDNA molecules. Thus, the Heparin-Binding Growth Factor (HGBF) cDNAs at issue in Bohlen were held to be unobvious despite the disclosure of the N-terminal portion of HGBF in one of the prior art references. Therefore, the claimed nucleotide sequences are currently being rejected as obvious over art references that disclose significantly less information regarding the protein than was disclosed by the cited art in Deuel.

In its review of the relevant case law, the Deuel Court observed that obviousness of a new chemical entity had always depended on whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. In Deuel, the prior art did not disclose any relevant cDNA molecules, let alone close relatives of the specific, structurally defined cDNA molecules of the claimed invention. Id. at 1558. Particularly, the Deuel Court indicated that

> while the general idea of the claimed molecules, their function, and their chemical structure may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of claims 5 and 7 would not have been obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules. (Id. at 1558)

Translating the Deuel reasoning to the claimed invention and cited art, it is apparent from the '203 patent that a hybridoma existed that contained some gene that encodes the LM609 non-human antibody. However, the precise cDNA molecules of LM609 are unobvious over the Brooks patent in view of gene cloning methods known in the art at the time the invention was made. In this regard, the Deuel Court clearly stated its rationale that

> one could not have conceived the subject matter of claims 5 and 7 based on the cited prior art because, until the claimed molecules were actually isolated and purified it would have been unlikely for one of ordinary skill to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious. (Id.)

In this context, the issue becomes whether the Brooks '203 patent and the known art of gene cloning and expression strategies for deriving recombinant antibodies disclose enough information regarding the claimed sequences to suggest to the skilled artisan the particular cDNA molecules of LM609. Significantly, like the claims at issue in Deuel, Applicant's claims recite specific compounds. Clearly, one of ordinary skill in the art could not

have conceived the claimed sequences based on the disclosures of the Brooks '203 patent and that which was known in the art regarding gene cloning and expression strategies for deriving recombinant antibodies. At most, the cited art would have motivated one of ordinary skill to search for the claimed sequences. According to Deuel, that is not enough to render the claimed sequences obvious:

> [The PTO theory] also ignores the fact that claims 5 and 7 are limited to specific compounds, and any motivation that existed was a general one, to try and obtain a gene that may have constituted many forms. A general motivation to search for some gene does not render obvious a specifically-defined gene that is subsequently obtained as a result of that search. More is needed and it is not found here. (Id.)

The Deuel court indicates that the claimed gene may have constituted many forms based on the prior art disclosure of the N-terminal portion of the protein. Applicant respectfully submits that, based on the lack of disclosure in the cited art of even a fragment of the amino acid sequence, the claimed sequences may have constituted many more forms than those at issue in Deuel.

The Examiner's argument that methodology exists which allegedly permits one skilled in the art to obtain the nucleotide sequence of an antibody based on the existence of constant regions ignores the clear mandate of Deuel:

> We affirm today the principle, stated in Bell, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed cDNAs.... A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. (Id. at 1559)

Moreover, the Examiner has previously cited In re Cofer, 354 F.2d 664 (CCPA 1966) as support for the proposition that a "compound may be defined or described by characteristics other than its chemical structure." (see Paper No. 8, page 7, second full paragraph). Applicant suggests that a more precise interpretation of the Cofer decision is that a compound may be defined or described by other characteristics in addition to its particular chemical structure or form.

The issue in Cofer was whether the claimed product, the free-flowing and crystalline form of a compound was rendered obvious by disclosure of its normal viscuous liquid state in the prior art. The Cofer Court held that the same compound described in the prior art in its normal state was unobvious in its crystalline form. Thus, a closer look at Cofer reveals that this case supports the proposition that obviousness requires a suggestion in the prior art of the particular structure or form of the compound or composition in question. The Cofer Court indicated that

> other factors [which] must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the particular compound or form of the compound or composition as well as suitable methods of obtaining that structure or form. (Id. at 668)(emphasis added)

Therefore, Cofer does not suggest that the lack of disclosure of the particular structure of a compound in the prior art can be compensated for by a suggestion of suitable methods for obtaining the claimed structure. Rather, Cofer indicates that both the particular compound or form of the compound and suitable methods of obtaining the compounds be considered.

Furthermore, the Examiner has asserted that In re Goldgaber, 41 U.S.P.Q.2d 1172 (Bd.Pat.App.& Interf. 1995) also belongs to the body of law supporting the notion that in the context of obviousness, a product can be described by the process of making it. Applicant notes that Goldgaber was decided by the Board of Patent Appeals and Interferences, a body that has no standing to overrule the controlling Deuel holding issued by its reviewing court.

The Goldgaber decision of finding that the claimed Alzheimer's Amyloid Polypeptide (AAP) cDNA was obvious over the prior art rested on two main arguments. First, the Goldgaber Board indicated that a person of ordinary skill in the art would have been motivated to isolate cDNA coding for AAP. Id. at 1173. In this regard, the Deuel Court stated that in order to render obvious a specifically defined gene "more is needed" than a

general motivation to search. (Deuel at 1558; see also discussion of Deuel, supra). According to Goldgaber, "more" was disclosed in the prior art that was found to render the AAP cDNA obvious. Specifically, as a second argument for finding obviousness, the Goldgaber Board indicated that the prior art put a person of ordinary skill in possession of the "key to success" by disclosing two sets of fully degenerate nucleic acid probes. In this regard, the Goldgaber Board attempted to distinguish the Deuel and Bell cases by pointing out that the prior art at issue discloses more than just the amino acid sequence of AAP. In contrast, the art cited in the above-identified application discloses not even the amino acid sequence of the LM609 antibody, much less provides a "key to success" for finding any of the claimed sequences.

Applicant respectfully submits that the Goldgaber Board misinterprets the legal mandate its reviewing court articulated in Deuel. Nevertheless, even when viewed within the framework of Goldgaber, the facts of the above-identified application are so distinct as to render Goldgaber inapplicable. In this regard, the overriding theme of Goldgaber is, at most, that of a "roadmap" leading from the prior art to the claimed sequences:

> In a nutshell, the combined disclosures of Glenner and Huynh provide a roadmap which would have directed a person having ordinary skill in the art to isolate DNA encoding the beta-amyloid polypeptide associated with Alzheimer's disease. That roadmap, we believe, would have led inevitably to a clone of DNA meeting the limitations of claim 4.

It is explicitly "on these facts" of a roadmap that the board reached its finding of obviousness. Id. at 1174. Where the Goldgaber prior art provided a "roadmap," the cited art in the above-identified application provides no roadmap to Applicant's claimed invention. On the most basic level, the prior art in Deuel provided a partial amino acid sequence of the protein and was held to be insufficient to support a finding of obviousness when combined with general cloning methods. In Goldgaber, disclosure of the complete amino acid sequence of AAP along with 128 degenerate nucleotide probes in combination with a secondary reference disclosing textbook details as to how to use the disclosed probes to isolate cDNA sequence of interest form a cDNA library was held sufficient to render obvious the claimed nucleotide sequence. By disclosing not even the amino acid sequence of LM609, the cited art in the above-identified application discloses less than the cited art held insufficient in Deuel, and it is insufficient to render obvious the specific sequences claimed under either the Deuel or the Goldgaber standards.

Moreover, in light of the difficulties described in the cited art for cloning authentic cDNA encoding a monoclonal antibody expressed by a hybridoma cell, as described above and corroborated by the Declaration by Dr. Huse (Exhibit 2), one skilled in the art would have had no expectation of readily obtaining the LM609 encoding nucleic acids using routine experimentation, as alleged in the Office Action. Therefore, Applicant respectfully maintains that Brooks et al., alone or in combination with the known art for cloning an immunglobulin gene

encoding a monoclonal antibody expressed by a hybridoma cell, does not teach or suggest nucleic acids encoding the parental non-human LM609 or the claimed LM609 CDR-grafted antibody and encoding nucleic acids.

In regard to the assertion on page 9, second paragraph of the Office Action, Applicant refers to the discussion above directed to the rejection under 35 U.S.C. § 112, second paragraph, for the meaning of "a modification thereof that does not change the encoded amino acid sequence." The claims specifically recite the nature of the modification of the claimed nucleic acid, that the modification of the nucleotide sequence does not change the encoded amino acid sequence, as described above. Furthermore, Applicant submits that the recited functional fragments of the claimed antibodies would not have been obvious in view of the cited art regarding generating humanized LM609-specific antibodies.

In summary, Applicant respectfully maintains that the claimed antibodies and nucleic acids having the structural features specifically recited in the claims as SEQ ID NOS are unobvious over Brooks et al., alone or in view of the known art for cloning immunoglobulin genes from a hybridoma cell. Therefore, the rejection of the claims under 35 U.S.C. § 103 is respectfully requested to be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

June 7, 2000
Date

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Inventor: William D. Huse
Serial No.: 08/790,540
Filed: January 30, 1997

EXHIBIT 1

PATENT
Our Docket: P-IX 2405

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: William D. Huse	Group Art Unit: 1644
	Examiner: P. Gambel
Serial No.: 08/790,540	
Filed: January 30, 1997	
For: ANTI-$\alpha_v\beta_3$ RECOMBINANT HUMAN ANTIBODIES, NUCLEIC ACIDS ENCODING SAME AND METHODS OF USE	

Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Sir:

I, William D. Huse, declare as follows:

1) I am the William D. Huse named as the inventor on the above-identified patent application.

2) I understand that the claims of the subject application stand rejected, in part, because Applicant allegedly did not invent the claimed subject matter.

3) I, William D. Huse, am the inventor of the claimed LM609 CDR-grafted antibody and encoding nucleic acids.

4) Dr. Cheresh, who was employed at the Scripps Research Institute, was contacted to discuss obtaining the hybridoma producing the LM609 mouse antibody. Dr. Brooks worked in Dr. Cheresh's laboratory at the Scripps Research Institute. An agreement was reached with the Scripps Research Institute of La Jolla, California to obtain the hybridoma producing the mouse LM609 antibody. The LM609 hybridoma was brought to Ixsys, Inc., where the LM609 heavy and light chain variable region cDNA was cloned. LM609 grafted antibodies were generated and developed having $\alpha_v\beta_3$ inhibitory activity. The sequences of the claimed antibodies and encoding nucleic acids were not known prior to cloning and sequencing of the LM609 heavy and light chain variable region cDNA and generation of LM609 grafted antibodies at Ixsys.

5) Dr. Cheresh was retained for technical advice on integrin biology. Neither Dr. Cheresh nor Dr. Brooks suggested or contributed to the cloning, sequencing, humanizing or making of the claimed antibodies and nucleic acids. In my opinion, Dr. Cheresh and Dr. Brooks were not inventors of the claimed antibodies and nucleic acid sequences.

6) Therefore, while at Ixsys, Inc., I conceived the claimed LM609 CDR-grafted antibody and encoding nucleic acids without contribution by other parties. As such, I believe I am the inventor of the claimed LM609 CDR-grafted antibody and encoding nucleic acids.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Date: 6/7/00

By: _____
William D. Huse

Inventor: William D. Huse
Serial No.: 08/790,540
Filed: January 30, 1997

EXHIBIT 2

PATENT
Our Docket: P-IX 2405

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: William D. Huse	Group Art Unit: 1644
	Examiner: P. Gambel
Serial No.: 08/790,540	
Filed: January 30, 1997	
For: ANTI-$\alpha_v\beta_3$ RECOMBINANT HUMAN ANTIBODIES, NUCLEIC ACIDS ENCODING SAME AND METHODS OF USE	

Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Sir:

I, William D. Huse, declare as follows:

1) I am the William D. Huse who is named as an inventor on the above-identified patent application.

2) I understand that the claims of the subject application stand rejected, in part, as allegedly obvious over Brooks et al., U.S. Patent No. 5,753,230, in view of the art related to gene cloning and expression strategies for generating recombinant antibodies.

3) A variable region heavy and light chain nucleotide sequence cannot be readily obtained from a hybridoma cell using polymerase chain reaction (PCR) primers with an expectation that the amplified sequence encodes the monoclonal antibody expressed by the hybridoma. A variety of problems involving the use of PCR primers to amplify a cDNA encoding an antibody expressed by a

hybridoma provides uncertainty with respect to obtaining authentic cDNA sequence encoding the antibody. For example, the PCR primers will introduce a mutation into the amplified sequence unless the PCR primers exactly correspond to the authentic sequence, and such mutations can inactivate the antibody. Secondly, the use of PCR itself can introduce mutations into the amplified sequence due to errors incorporated by the polymerase. Thirdly, PCR primers do not amplify from the ends, resulting in truncations. Additionally, hybridoma cells often express more than one heavy chain RNA, which are generated from unproductive rearrangements, resulting in the amplification of multiple species by PCR. Moreover, fusion partners used to generate the hybridoma can also contribute RNA that does not encode the monoclonal antibody, for example, RNA expressed from a myeloma cell used as a fusion partner, which can similarly result in the amplification of multiple species. Finally, some sequences are difficult to amplify with PCR primers from a consensus framework region. In some cases, the authentic sequence may never be amplified using PCR primers. Therefore, the use of PCR primers from consensus framework sequences or other conserved sequences to amplify RNA expressed in a hybridoma cell provides no guarantee that one would obtain the authentic sequence encoding the monoclonal antibody produced by the hybridoma without further characterization, in particular, functional characterization of the antibody encoded by the amplified sequence.

4) Due to the expected difficulties involved in cloning authentic cDNA sequence encoding LM609 using PCR primers to conserved sequences, the claimed nucleic acids were obtained by generating PCR primers based on the first six amino acids in each variable chain. The six N-terminal amino acids from each variable chain were determined by N-terminal amino acid sequencing of purified LM609 antibody. The determined amino acid sequences were used to design forward PCR primers encoding the first six amino acids of each antibody variable chain. These primers were used to amplify heavy and light chain variable regions of LM609.

5) In conclusion, I believe that, due to the difficulties associated with cloning and determining the authentic nucleotide sequence encoding a monoclonal antibody expressed by a hybridoma cell, there would have been no expectation of success that using PCR primers to a consensus framework or other conserved sequence would allow one to reliably obtain the sequence of LM609 variable regions from the LM609 hybridoma with or without further experimentation to determine which of any sequence obtained corresponded to authentic LM609 nucleic acid sequence.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Date: 6/7/00 By: _____
William D. Huse

US 087905400IP1

Creation date: 01-12-2004
Indexing Officer: LCHAU - LINH CHAU
Team: OIPEScanning
Dossier: 08790540

Legal Date: 09-23-1999

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Remarks:

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